NAPM

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October 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

This citizen petition is submitted by the National Association of Pharmaceutical Manufacturers (NAPM), pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and 21 C.F.R. § 10.30. This petition requests that the Food and Drug Administration (FDA) maintain the long-standing agency position and continue to approve abbreviated new drug application (ANDA) suitability petitions, without regard for whether a pediatric study may be required under 21 C.F.R. § 201.23, "Required Pediatric Studies," as adopted in the Federal Register for December 2, 1998, 63 Fed. Reg. 66,632. NAPM does not believe that final rule should have any effect on the review and approval of ANDA suitability petitions.

NAPM is the national trade association representing generic drug manufacturers and suppliers of bulk active drug substances and related goods and services to this industry.

99P-4618

CP1

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A. Action Requested

NAPM requests that FDA review, and approve where appropriate, ANDA suitability petitions seeking a change in strength, dosage form, active ingredient, or route of administration, in accordance with the principles in place before the December 2, 1998 pediatric studies final rule, even if the proposed drug product would ultimately require a pediatric study under § 201.23. We request that FDA retract the following statement in the preamble to that final rule:

> FDA notes that [ANDA suitability petitions under section 505(j)(2)(c) of the FFDCA] may be denied if "investigations must be conducted to show the safety and effectiveness of" the change. Thus, if a petition is submitted for a change that would require a pediatric study under this rule, the petition may be denied.

63 Fed. Reg. at 66,641.

NAPM further requests that in those instances where a pediatric study may be deemed necessary under § 201.23, submission of the study be deferred until after an ANDA has been submitted and approved for the proposed product. The deferral of a pediatric study should be based on the ANDA applicant's submission of a protocol for the study (or a request for a waiver

from the study requirement pursuant to § 201.23) before approval of the ANDA, accompanied by the applicant's commitment to perform the study (unless waived) within a reasonable, specified time period after ANDA approval.

B. Statement of Grounds

The goal of FDA's pediatric studies rule is the development of appropriate product labeling, based on clinical studies, regarding drug usage in different pediatric subpopulations. NAPM supports this important public health goal.

As proposed (62 Fed. Reg. 43,900; Aug. 15, 1997), the pediatric studies rule only would have required an application for a drug classified as a new chemical entity to contain safety and effectiveness information on relevant pediatric age groups for the claimed indications. However, after reviewing comments, FDA issued a final rule that "expands the scope of the rule to include . . . new dosage forms, new dosing regimens and new routes of administration for which an applicant is seeking approval." 63 Fed. Reg. at 66,634. Thus, unlike the proposed rule, the final rule has the effect of precluding FDA from approving ANDAs for drugs that differ in route of administration, dosage form, or strength from the reference listed drug (RLD) unless the ANDA

sponsor performs pediatric clinical trials of the modified product (or unless the modified product does not represent a meaningful therapeutic benefit, and is unlikely to be in substantial use, for pediatric patients).

While fully supporting FDA's goal of developing pediatric labeling, NAPM has serious concerns about the appropriateness of this expansion of the rule. Under the FFDCA, as amended in 1984 by the Drug Price Competition and Patent Term Restoration Act (commonly known as the Hatch-Waxman Amendments), once a brand name manufacturer obtains approval for a particular drug product and relevant periods of patent protection and nonpatent market exclusivity for that product expire, another drug manufacturer is entitled to gain approval to market a generic version of the same product upon submission of an ANDA that establishes that its drug product is bioequivalent to the brand name product. In general, an ANDA product must be the "same as" the RLD referred to in the ANDA in dosage form, route of administration, and strength. Section 505(j)(2)(C) of the FFDCA provides for ANDA suitability petitions for changes from the RLD in route of administration, dosage form, or strength, unless FDA finds that "investigations must be conducted to show the safety and effectiveness of the drug."

As noted above, FDA stated in the preamble to the pediatric studies final rule that "if [an ANDA suitability] petition is submitted for a change that would require a pediatric study under

this rule, the petition may be denied." 63 Fed. Reg. at 66,641 (emphasis added). However, based upon our conversations with FDA staff and FDA's September 16, 1999 decision to rescind approval of an ANDA suitability petition for omeprazole delayed-release tablets (discussed below), it appears that FDA's view of the effect of the rule is that a petition must be denied if it is submitted for any change in route of administration, dosage form, or strength for a drug that may have utility in pediatric populations. Thus, as FDA is interpreting it, the pediatric studies rule has the effect of reading the ANDA suitability petition provision out of the FFDCA.

Because the agency apparently interprets the pediatric studies rule to require it to deny ANDA suitability petitions in all cases where a new dosage form, strength, or route of administration is sought for an approved drug (unless the drug does not represent a meaningful therapeutic benefit for pediatric patients and is unlikely to be used by a substantial number of them), the rule has the effect of creating a presumption that investigations are necessary to show the safety and effectiveness of such a modified drug product. See 63 Fed. Reg. at 66,634 and 66,645. This presumption will delay innovation by generic manufacturers, and could hinder -- if not stop -- the development of "child friendly" dosage forms (such as liquids, based on the brand name tablet or capsule) because many generic manufacturers do not have either the expertise or the resources to conduct clinical studies.

NAPM objects strenuously in principle to the notion that manufacturers of generic drugs should be required to conduct clinical trials of the safety or efficacy of products that are variations of previously approved brand name products. NAPM believes this burden should rest with the sponsor of the approved brand name product, which does have the expertise and resources to conduct pediatric clinical studies. Nevertheless, it is not necessary for FDA to address this fundamental concern in responding to this petition. NAPM's members are willing, where necessary and appropriate, to conduct pediatric studies as required by the December 1998 rule. For the reasons explained below, however, NAPM requests that the agency not deny ANDA suitability petitions merely because such studies may be necessary. Rather, the agency should permit ANDA sponsors to defer submission of such studies until after the ANDA has been submitted and approved.

Since the passage of the Hatch-Waxman Amendments, FDA has reviewed more than 700 ANDA suitability petitions. An overwhelming majority of the ANDA suitability petitions submitted to FDA have sought a change from either the strength or the dosage form of the RLD. Many requests for dosage form changes have been for a change from one solid oral dosage form to another (tablet to capsule or vice versa), or from a solid oral dosage form to a liquid dosage form or a chewable or orally disintegrating form. The reason most often given for the latter type

of change is to provide a dosage form that is more convenient for those patients who may not be able to swallow a tablet or capsule. This group includes infirm patients, the elderly, patients with a nasal or gastric feeding tube, and, of course, children.

In evaluating such ANDA suitability petitions, the agency has always considered whether the proposed modified product would likely be used in pediatric patients. If that likelihood existed, the agency evaluated the labeling of the RLD to determine whether it provided appropriate dosing and other instructions for the product's safe and effective use in pediatric patients. If there was a likelihood of the proposed product's use in children, but there was no pediatric labeling for the RLD (e.g., the labeling of the RLD stated not to use the drug in children), then the petition was routinely denied. NAPM does not take issue with this long-standing agency policy.

However, NAPM is concerned that the December 2, 1998 final rule and other recent developments in relation to pediatric labeling exclusivity may be having a significantly negative impact on the ANDA suitability petition process. Recent FDA activity appears to identify more broadly those drugs that may have a possible pediatric use, as evidenced by the very comprehensive nature of the List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in Pediatric Populations (Pediatric Drug List). NAPM is also concerned about the degree to which FDA is relying on pediatric subgroups in determining those

products for which additional pediatric information may be needed. For example, FDA indicated in the preamble to § 201.23 that certain drug products would be useful in certain pediatric sub-age groups other than those already listed on the labeling, 63 Fed. Reg. at 66,631.

As noted, the preamble to the December 1998 final rule states that ANDA suitability petitions "may" be denied if pediatric studies are needed for the proposed product. Based on our informal discussions with agency personnel, it appears that FDA is going even further. For example, by letter dated September 16, 1999, FDA rescinded its previously granted approval of an ANDA suitability petition submitted by Andrx Pharmaceuticals, Inc., requesting permission to file an ANDA for omeprazole delayed-release tablets, 10 mg and 20 mg (docket number 98P-0225, Enclosure 1). The RLD was omeprazole delayed-release capsules, in the same strengths. As we understand FDA's rationale (based on discussions with FDA staff and language in the September 16 letter), the ANDA suitability petition was denied solely because omeprazole is included in FDA's Pediatric Drug List. FDA denied the ANDA suitability petition even though the proposed modified dosage form does not have any greater potential for pediatric usage than the approved brand name capsules.

NAPM does not believe that this is the most appropriate way in which to handle ANDA suitability petitions. The possible need for pediatric studies and pediatric labeling for a proposed

modified product should not have any effect on whether to approve an ANDA suitability petition. This process has served the public well since the 1984 passage of the Hatch-Waxman Amendments. The decisionmaking process to determine which suitability petitions are approved should not be affected by the goal of § 201.23 of promoting the study and inclusion of pediatric uses in drug labeling.

In particular, if the drug appears on FDA's Pediatric Drug List, an ANDA suitability petition seeking a dosage form that may be more amenable to pediatric use (e.g., change from a solid oral dosage form to a liquid) should be approved (if otherwise appropriate) whenever the labeling of the RLD provides use information for any pediatric sub-age group. The availability of the proposed generic product addressed by the ANDA suitability petition would benefit, at a minimum, pediatric patients in the identified sub-age group.

Some ANDA suitability petitions for changes in dosage form are not targeted at all at pediatric patients, nor would the change in any way promote additional use in the pediatric population. Examples of this type of dosage form change are tablet-to-capsule or capsule-to-tablet changes (e.g., the situation presented by the omeprazole ANDA suitability petition) and changes from a powder for injection to a solution for injection. In these cases, even if the drug appears on the Pediatric Drug List, an ANDA suitability petition should be approved (if otherwise

appropriate) without regard for whether the labeling of the RLD includes any pediatric use information since the product would be used no differently in any population than its current brand name counterpart.

If FDA concludes that a pediatric study is needed for a proposed generic product permitted by an approved ANDA suitability petition, NAPM recommends that the agency grant a deferral (or a waiver where appropriate) of the requirement to conduct pediatric studies until after an ANDA is approved. As a condition of approval, FDA would require the ANDA applicant to submit a satisfactory protocol for conducting a pediatric study, along with a commitment to conduct the study within a reasonable, specific time period after approval. In the event the ANDA sponsor does not live up to its commitment, FDA has the enforcement options set forth in § 201.23(d) and discussed in the rulemaking preamble, 63 Fed. Reg. at 66,636.

The bioequivalency, chemistry-manufacturing-controls, and labeling sections of an application submitted based on an approved ANDA suitability petition are most appropriately reviewed by FDA's Office of Generic Drugs (OGD). On the other hand, a clinical pediatric study is most appropriately reviewed by the appropriate new drug review division for the type of drug product in question. As Congress has recognized, if a proposed change from an RLD does not on its face require safety or efficacy studies to support approval of the change, then the agency

must approve the change, and the modified product is appropriate for submission, review, and approval (if appropriate) by OGD as an ANDA. If FDA determines that pediatric studies are needed under § 201.23, NAPM believes that the most appropriate format for the submission of such pediatric studies, following approval, is in the form of a 505(b)(2) supplement to the approved ANDA. In an April 10, 1987 letter to all NDA and ANDA holders and applicants (Enclosure 2), FDA stated that such supplements were permitted by agency policy. Since then, FDA has on a number of occasions reviewed and approved such supplements.

In this manner, a generic product in a different dosage form amenable to pediatric use can come to market promptly, and those segments of the adult or pediatric population identified in the labeling of the RLD can benefit immediately from its approval, while not undermining the agency's ability under § 201.23 to require further study in pediatric populations. Dosage form changes that do not appear to have the potential for increasing pediatric use should be approved regardless of whether the labeling of the RLD includes any pediatric use information.

C. Environmental Impact

This petition is entitled to a categorical exclusion under 21 C.F.R. § 25.30 and § 25.31.

D. Economic Report

NAPM will submit an economic analysis upon request.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views upon which the person relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Robert S Milanese 2YT

Robert S. Milanese
President

Enclosures

Enclosure 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 16

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 S.W. 47th Ave.
Ft. Lauderdale, FL 33314

Docket No. 98P-0225/CP1

Dear Ms. Servello:

This is to inform you of new regulations that will affect any Abbreviated New Drug Application (ANDA) you file on or after April 1, 1999 that relies on a suitability petition approved by the Agency before April 1, 1999. Specifically, on December 3, 1998, the Agency approved your petition filed on April 9, 1998, and amended April 29, 1998, requesting permission to file an ANDA for the following drug products: Omeprazole Delayed-release Tablets, 10 mg and 20 mg. The listed drug products to which you refer in your petition are Prilosec® (Omeprazole) Delayed-release Capsules, 10 mg and 20 mg manufactured by Astra Merck, Inc.

Your request involved a change in dosage form from that of the listed drug products (i.e., from delayed-release capsule to delayed-release tablet). The change you requested is the type of change that is authorized under the Act.

This petition was originally approved pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act). Under Section 505(j)(2)(C)(i) of the Act, a petition requesting a change in dosage form will be approved unless the Agency finds that investigations must be conducted to show the safety and effectiveness of the differing dosage form.

However, you did not file an ANDA based on your approved suitability petition before April 1, 1999, the effective date of the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, published , December 2, 1998, in the Federal Register (Pediatric Rule)(63 FR 66632). Therefore, the agency has reevaluated your petition with respect to the Pediatric Rule.The agency has determined that your proposed change in dosage form is subject to the Pediatric Rule and has concluded that investigations are necessary to demonstrate the safety and effectiveness of Omeprazole Delayed-release Tablets, 10 mg and 20 mg in the pediatric population (see Preamble to Pediatric Rule 63 FR 66640-41). Therefore, FDA is withdrawing the December 3, 1998, approval of your petition under 21 CFR 314.93(f) and is denying the petition under Section 505(j)(2)(C)(i) because investigations are necessary to show the safety and effectiveness of the proposed drug products. We suggest that you contact the Division of Gastrointestinal and Coagulation Drug Products at (301) 827-7310 for further information.

98P-0225

FDN 1

If you disagree with our determination concerning the acceptability of your petition as originally submitted, you may seek a reconsideration of the denial following the procedures set forth in 21 CFR 10.33. Requests for reconsideration must be based solely on the information contained in your original petition and must be submitted in accordance with 21 CFR Section 10.20, in the format outlined in Section 10.33 and no later than 30 days after the date of the decision involved. Petitions for reconsideration should be filed with the Dockets Management Branch at the address listed below. If there is additional information, not included as part of your original submission that you would like the Agency to consider, you should submit a new petition including all the necessary information to the Dockets Management Branch.

A copy of this letter withdrawing approval and denying your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

To all NDA and ANDA holders and applicants

APR 10 1987

Dear Sir or Madam:

This is another in a series of letters intended to provide informal notice to all affected parties of developments in policy and interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984. This letter deals with an issue about which a number of questions have arisen, namely the statutory mechanism by which ANDA applicants may make modifications in approved drugs if the modifications require the submission of clinical data. For example, an applicant may wish to obtain approval of a new indication for a listed drug that is only approved for other indications. If the applicant has an approved ANDA for the approved indications, agency policy permits the applicant to submit a supplemental application that contains reports of clinical investigations needed to support approval of the new indication. (Because such a supplement would require the review of clinical data, FDA would process it as a submission under section 505(b) of the Federal Food, Drug and Cosmetic Act.)

A similar case may arise where an applicant wishes to seek approval of a modification of an approved product but has no interest in marketing the drug in its originally approved form. Assuming that clinical data were required for approval, the statute could be interpreted to require such an applicant to first manufacture, and obtain approval of an ANDA for, the listed drug's approved form and then file a 505(b) supplement to the approved ANDA containing the clinical data to obtain approval of the modification. If the applicant did not first obtain an ANDA for the approved form, the applicant could be required to submit a full NDA for modification and duplicate the basic safety and effectiveness studies conducted on the listed drug.

FDA has concluded that such an interpretation is inconsistent with the legislative purposes of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Amendments), because it would serve as a disincentive to innovation and would require needless duplication of research.

FDA believes that a more consistent and less burdensome interpretation of the 1984 Amendments is to allow a generic applicant to submit a 505(b) "supplement" (a form of NDA) for a change in an already approved drug that requires the submission of clinical data, without first obtaining approval of an ANDA for a duplicate of the listed drug. This submission would include data only for those aspects of the proposed drug that differ from the listed drug. Changes in already approved drugs for which such applications will be accepted include changes in dosage form, strength, route of administration, and active ingredients for which ANDA suitability petitions cannot be approved because studies are necessary for approval as well as new indications. Like similar supplements to approved ANDAs, these applications will rely on the approval of the listed drug together with the clinical data needed to support the change. The applicant will thus be relying on the approval of the listed drug only to the extent that such reliance would be allowed under section 505(j): to establish the safety and effectiveness of the underlying drug.

FDA believes that it would be inconsistent with the policies of the 1984 Amendments to allow these applications to rely on the approval of a listed drug without due regard for the listed drug's patent rights and exclusivity. Therefore, an application that relies in part on the approval of a listed drug and in part on new clinical data will, for this purpose, be considered an application described in section 505(b)(2) and must contain a certification as to any relevant patents that claim the listed drug. In addition, the date of submission and effective approval of these applications may, under section 505(c)(3), be delayed to give effect to any patent or period of exclusivity accorded the listed drug.

Because these submissions will be reviewed as applications under section 505(b), they will be subject to the statutory and regulatory requirements applicable to such applications, including the patent filing requirements of sections 505(b) and (c). These submissions also may be eligible for three years of exclusivity under sections 505(c)(3)(D)(iii) and (iv) and 505(j)(4)(D)(iii) and (iv). These applications should be submitted to the appropriate review division in CDRR/CBRR for review and final action.

Sincerely yours,

Paul D. Parkman, M.D.
Acting Director
Center for Drugs and Biologics